REMARKS

Claims 1-36 have been canceled without prejudice. New claims 37-60 are supported by the as-filed claims and by the Specification (Tables 8, 10 and 18; SEQ ID NO::16, 19 and 45). Applicants reserve the right to pursue any subject matter that has not been presented herein in a future application. Former claim 9, which previously depended from claim 1, has been rewritten in independent form as new claim 37 and now incorporates all of the limitations of claims 1 and 9. This amendment was made to expedite prosecution, the Examiner having indicated that this subject matter is allowable. In new claims 42, 45, 47, 53, 56 and 59, the references to protein sequences including N-terminal His-tags have been amended so that the complete proteins and the portions of these proteins without the His-tags are claimed. This amendment is supported for example at page 23, lines 9-14, page 31, line 26 to page 32, line 4 and page 33, lines 6-8, where it is clear that the His-tag portion of the protein is optional. Claims 59-60 are drawn to tandem repeat membrane scaffold proteins. This is supported by Tables 8, 10 and 18 and the corresponding sequences in the Sequence Listing. None of the amendments made herein constitutes the addition of new matter.

The Interview Summary

Applicants appreciate the time and advice provided by the Examiner and his Supervisor in the personal interview held February 2, 2004. The differences between the present invention and the cited art and the allowable subject matter were discussed. Applicants have endeavored to provide new claim language in accordance with the strategy discussed in the interview.

The MSP2 protein (SEQ ID NO:17) had been found allowable. The Patent Office had suggested presenting a claim to a genus of membrane scaffold proteins that could be found allowable. Claim 59 is drawn to a tandem repeat membrane scaffold protein and claim 60 recites the three particular examples of tandem repeat membrane scaffold proteins from the application (SEQ ID NOs:17, 19 and 45 and the portions of same

lacking the N-terminal 12 amino acid histidine tags). In accordance with the discussion with the Patent Office, claims to nanoscale particles comprising a tandem repeat membrane scaffold protein and a tethered membrane protein have been presented, as well as claims to a method of making such a nanoscale particle. Favorable consideration of these claims is respectfully requested. The protein with SEQ ID NO:17 has already been found allowable. In addition, the Patent Office discussed claims to nanoscale particles comprising any membrane scaffold protein together with an integral membrane protein or an embedded membrane scaffold protein and such claims have been presented along with corresponding method of making claims.

Claim Objections

Claims 8, 18, and 19 were objected to because they recite nonelected subject matter, the amino acid sequences set forth in SEQ ID NOS: 6, 9, 19, 23, 29, 43-45.

With respect to claims related to nanoscale particles and methods related to tethered membrane proteins, the new claims are limited to the use of a tandem repeat membrane scaffold protein having the amino acid sequence set forth in SEQ ID NO:17, which had been identified as allowable. In anticipation of allowability of claims to tandem repeat membrane scaffold proteins and their uses in methods and particles, these claims recite membrane scaffold proteins of SEQ ID NO:17, amino acids 13 to amino acids 13 to 414 of SEQ ID NO:17, SEQ ID NO:19, amino acids 13 to 422 of SEQ ID NO:19, SEQ ID NO:45 and amino acids 13 to 392 of SEQ ID NO:45.

Claims 14-17 were objected to as being dependent on a rejected base claim. New claim 37 is drawn to a nanoscale particle comprising a membrane scaffold protein and an integral membrane protein. Dependent claims 38-43 are drawn to particular types and examples of integral membrane proteins and with respect to the membrane scaffold protein, various engineered membrane scaffold proteins and apolipoprotein A1. Applicants have also provided a set of method claims identical in scope to those in the claims to particles comprising a membrane scaffold protein and an integral membrane

protein. Similarly, in accordance with the discussion with the Examiner in the personal interview, Applicants have presented a set of new claims drawn to nanoscale particles and methods of incorporating an embedded membrane protein in a nanoscale particle.

A set of claims was presented to cover a nanoscale particle comprising a tethered membrane protein and a tandem repeat membrane scaffold having the amino acid sequence set forth in SEQ ID NO:17 (MSP2), amino acids 13 to 414 of SEQ ID NO:17, SEQ ID NO:19, amino acids 13 to 422 of SEQ ID NO:19, SEQ ID NO:45 or amino acids 13 to 392 of SEQ ID NO:45, and methods with the same scope of membrane scaffold protein. The sequences of other specifically exemplified tandem repeat membrane scaffold proteins are also recited in claim 60; claim 59 recites the use of a tandem repeat membrane scaffold protein. Accordingly, Applicants submit that claims are in condition for allowance. Applicants recognize that there has been a restriction requirement with respect to membrane scaffold proteins and particles; however, rejoinder with claims of the same scope as were indicated as allowable is respectfully requested.

Claim 60 has been presented; it is drawn to a membrane scaffold protein having the amino acid set forth in SEQ ID NO:17, which has been deemed allowable, as well as other exemplary tandem repeat membrane scaffold proteins with or without a His tag at the N-terminus. Support for proteins lacking the His tag is discussed herein above. Claim 59 is drawn to the genus of tandem repeat membrane scaffold proteins. Support is found in Tables 8, 10 and 18.

Withdrawal of the objections to the claims is respectfully requested.

The Rejections under 35 U.S.C. § 102(b)

Claims 1-7, 9, 10, and 13 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bayburt *et al.* Applicants respectfully traverse this rejection.

With regard to Applicants' assertion that the amended claims which recite an "artificial" membrane scaffold proteins are distinct in their amino acid sequences from an apo AI protein as disclosed in Bayburt *et al.* has not been deemed to be persuasive because a membrane scaffold protein, *e.g.,* apo AI protein can be made by DNA recombinant technology and such an artificial scaffold protein can have the same sequence as that of a membrane scaffold protein isolated from a natural source. The Examiner also asserts that the specification fails to unambiguously define an artificial scaffold membrane protein as one that has a distinct amino acid sequence from a naturally occurring scaffold membrane protein. The Examiner concludes that the word "artificial" does not limit the scope of the claimed invention and that the Bayburt *et al.* reference still reads on the limitations of claims 1-7, 9, 10, and 13.

Applicants respectfully request reconsideration because the protein and particles described by Bayburt *et al.* differ from those presently claimed. However, it is clear from the context of the specification as filed, that the word "artificial" means, *inter alia*, that the membrane scaffold proteins of the present invention have amino acid sequences that are different from the naturally occurring amino acid sequences. "Artificial" is not intended to be, in effect, a process limitation. That is, it is not intended to refer to how the protein is made, *i.e.,* by recombinant technology. The specification gives numerous non-limiting examples of the kinds of differences between natural apoAI and the artificial membrane scaffold proteins of the present invention. For example, the specification describes artificial membrane scaffold protein, sequences in which certain helices of native apoAI are repeated, deleted or replaced with other helices, or have truncations, or have altered hinge regions. See also pages 14, 19 and 28-29 of the as-filed specification. Because Bayburt *et al.* does not teach such modifications of apoA1, it cannot properly be found to anticipate claims 1-7, 9, 10, and 13, and therefore the rejection should be withdrawn. Where the membrane protein incorporated into a nanoscale particle, the membrane scaffold protein is a **tandem repeat** membrane scaffold protein.

However, in the interest of advancing prosecution and without acquiescing to the rejection, new claims 37-46 are drawn to nanoscale particles comprising membrane scaffold protein and at least one integral or embedded membrane protein. The Bayburt reference relates to cytochrome P450 reductase, a tethered membrane protein. Those claims (47-48) drawn to nanoscale particles (and methods) comprising a tethered membrane protein are limited to the use of the membrane scaffold protein (MSP2)as set forth in SEQ ID NO:17, which was said to be allowable, as well as other tandem repeat membrane scaffold proteins. The cited Bayburt reference relates to an apolipoprotein AI protein which is not a tandem repeat membrane protein. Compare, e.g., Tables 2 and 8 of the as-filed application. As discussed in the personal interview, there was no teaching or suggestion in the cited Bayburt reference that an embedded or integral membrane protein could be incorporated into a nanoscale particle, where the protein is maintained in an active conformation, like that of the native protein in a natural membrane environment.

Claims 1-7 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Frank *et al.* (*Biochemistry* 36:1798-1806 (1997)). Applicants respectfully traverse this rejection.

The Examiner characterizes Frank *et al.* as teaching a recombinant wild-type human (His apo A1) expressed in *E. coli* with an N-terminal extension of 11 residues and 3 apoAI mutants. The Examiner further asserts that Frank *et al.* teaches that the His-apoAI exhibits similar physical chemical properties to a native apoAI and can form homogeneous discoidal apoA1-containing particles with phospholipids which exhibits size ranges from 9.5 to 10.5 nm. The three mutants described by Frank *et al.* also allegedly demonstrate a property of forming homogeneous discoidal apoA1-containing particles that are of slightly smaller size.

The Examiner also alleges that the membrane scaffold proteins taught by Frank *et al.* which are either native or artificial, would by their nature form a nanoscale particle

with at least one hydrophobic or partially hydrophobic protein as recited in claim 4. Further, the Examiner asserts that the membrane scaffold proteins would also form a nanoscale particle as recited in claims 5-7 in the presence of amphipathic lipid molecules other than phospholipid. The Examiner thus concludes that the cited Frank et al. reference meets the limitations of claims 1-7.

With respect to the rejection of claim 4, as allegedly anticipated by Frank *et al.*, Applicants respectfully submit that Frank *et al.* fails to teach the combinations of any additional hydrophobic or partially hydrophobic protein, such as a tethered, embedded or integral membrane protein along with the artificial membrane scaffold protein to give rise to a nanoscale particle between about 5 nm and 500 nm in diameter as called for by claim 4 (now as claims 37-48). Because Frank *et al.* fails to teach the combination of an additional, partially hydrophobic or hydrophobic protein with the artificial membrane scaffold protein as is presently claimed, it cannot properly anticipate the claims and therefore the rejection of claim 4 under 35 U.S.C. § 102(b) should be withdrawn.

With respect to the rejection of claims 5-7 in view of Frank *et al.*, the Examiner stated that the membrane scaffold protein of Frank *et al.* would also form a nanoscale particle as recited in claims 5-7 in the presence of amphipathic lipid molecules, *e.g.*, cholesterol, and glycolipids other than phospholipids.

Applicants respectfully argue that because Frank *et al.* does not teach or suggest nanoscale particles between about 5 nm and about 500 nm comprising any membrane protein as now claimed (claims 37-48), these claims are not anticipated. With respect to the particular membrane proteins now claimed (claims 59-60), the cited Frank reference does not teach any tandem repeat membrane scaffold proteins. Compare the claimed sequences (Tables 8, 10, 18) against those of the cited Frank reference. Because Frank *et al.* fails to teach proteins and particles as claimed, Applicants respectfully submit that the reference does not properly anticipate the invention as now claimed.

Request to Rejoin Nonelected Species

In the Restriction Requirement mailed on March 24, 2003, Applicants were required to elect a species for prosecution in connection with claims 11-13 because the claims are allegedly directed to three species of membrane protein: a tethered membrane protein, an embedded membrane protein, and an integral membrane protein (all in association with a membrane scaffold protein in a nanoscale particle), which were deemed by the Examiner to be patentably distinct. Restriction to a single species was required for further prosecution if no generic claim was held to be allowable. In response, Applicants elected "integral membrane proteins."

As discussed above, Applicants have presented new claims 37-43, which are drawn to nanoscale particles comprising integral membrane proteins in conjunction with membrane scaffold proteins. Claims 44-46 are drawn to nanoscale particles comprising embedded membrane proteins in conjunction with membrane scaffold proteins, and claims 47-48 are drawn to nanoscale particles comprising tethered membrane proteins in conjunction with membrane scaffold proteins. Applicants submit that in view of the amendments to the claims and for the reasons discussed above, taking the advice of the Examiner and his supervisor into account, the claims now presented are believed allowable. Applicants request withdrawal of the requirement for election of a single species of membrane protein and request rejoinder and reconsideration of claims directed to embedded membrane proteins, as well as tethered membrane proteins in conjunction with tandem repeat membrane scaffold proteins. Applicants have several embodiments of various membrane proteins incorporated into nanoscale particles, and they are entitled to claims of breadth commensurate with their contribution to the art.

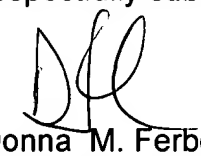
Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance and early notification thereof is requested.

If in the interest of expediting prosecution, the Examiner has questions or comments, he is invited to telephone the undersigned at the indicated telephone number.

This Amendment is accompanied by a Request for Continued Examination and a check in the amount of $385.00, as required by 37 C.F.R. 1.17(e). It is believed that the present Amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If this is incorrect, however, please charge any fees due pursuant to the Rules to Deposit Account No. 07-1969.

Respectfully submitted,



Donna M. Ferber
Registration No. 33,878

GREENLEE, WINNER AND SULLIVAN, P.C.
5370 Manhattan Circle, Suite 201
Boulder, CO 80303
Telephone (303) 499-8080
Facsimile: (303) 499-8089
Email: winner@greenwin.com

Attorney Docket No.: 87-00
bmk: March 1, 2004